PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: KORENBERG, JULIE R.	EXAMINER: SWITZER, JULIET CAROLINE
APPLICATION NO.: 08/956,991	ART UNIT: 1634
FILED: OCTOBER 23, 1997	CONF. NO: 9464
FOR: **NUCLEIC ACID ENCODING DS-CAM PROTEINS AND PRODUCTS RELATED THERETO**	

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Declaration under 37 C.F.R. § 1.132 by Julie Korenberg

1. I, Julie R. Korenberg of 8125 Skyline Drive, Los Angeles, CA 90046, hereby declare as follows:

2. I am currently a Professor of Human Genetics and Pediatrics at University of California Los Angeles and Vice-Chair of Pediatrics for Research at Cedars-Sinai Medical Center. I received a bachelor degree in Genetics from McGill University in 1968 and a Ph.D. degree from University of Wisconsin Madison in 1976. I have published more than 140 peer-reviewed articles.

3. I am the sole inventor of the above-identified application.

4. I have reviewed the present application (the "Specification"), the pending claims, the Final Office Action mailed November 19, 2003, the Advisory Action mailed March 24, 2004, and the Interview Summary mailed April 15, 2004.

5. I understand that the pending claims have been rejected as not meeting the utility requirement. In particular, the Advisory Action states that a review of the literature did not identify such a well known utility for the DS-CAM

nucleic acid molecules utility as a diagnostic marker for Down Syndrome (DS). I understand that the utility rejections were based on this statement, with which I respectfully disagree.

6. I participated in a telephonic interview with Examiner Switzer on April 12, 2004. During the interview I was asked to clearly point out how the specification and prior art references support the utility of the claimed DS-CAM as a marker for the detection of DS through the filing of a Request for Continued Examination and a declaration.

7. Prior to the earliest filing date of the present application, it was well known in the art that Band q22 of Chromosome 21 was called the "Down Syndrome region", and that duplication of this region was associated with the major phenotypic features of DS including metal retardation, congenital heart disease, the characteristic facial appearance, and probably the DS hand anomalies and dermatoglyphic changes. Korenberg et al., Am. J. Hum. Genet. 47: 236 – 246 (1990)(Exhibit 1, p. 236, down right corner). Accordingly, without the trisomy of Band q22 of Chromosome 21, the above-mentioned clinical features of DS would not be manifested.

8. The SOD1 gene, a cloned gene located in the DS region prior to 1990, "had assumed the role of being a "molecular marker" of DS", although its contribution to the DS phenotype was unknown. (Exhibit 1, p. 237, up-left corner). Therefore, at least as early as 1990, one of ordinary skill in the art would consider a gene which had been identified and cloned from the DS region as a molecular marker for DS.

9. Prior to the earliest filing date of the present application, it was well known in the art that protocols had been developed for the diagnosis of DS. Epstein et al., Am. J. Hum. Genet. 49: 207-235 (1991) (Exhibit 2). In particular, Epstein et al. taught:

> The protocols which have been developed were designed to provide a uniform and precise specification of the phenotype and degree of chromosome imbalance of each individual to be studies. Although they are not intended for use in the diagnosis or investigation of Down syndrome per se, these protocols should nonetheless prove useful for these purposes and possibly for the care of persons with Down syndrome.

Exhibit 2, p. 207, right column (*emphasis added*). In addition, Epstein et al taught protocols that "estimate the copy number of DNA sequences in aneuploid DNAs by comparing the signal from a sequence of unknown copy number with that of a reference sequence the copy number of which in the aneuploid DNA is known" (Exhibit 2, p. 211, left column). In

describing the Southern blot dosage analysis protocol, Epstein et al. stated:

> This technique allows the assessment of copy number of any unique chromosome 21 sequence. Southern blots are constructed with restriction enzyme-digested aneuploid and diploid DNAs, hybridized simultaneously with both a probe for a potential duplicated region of chromosome 21 and a reference probe, and the resulting band signals are measured by densitometry.

Exhibit 2, p. 211, left column (*emphasis added*). Epstein et al. emphasized that the technique is broadly applicable to the analysis of all DNA sequences (Exhibit 2, p. 211, right column). Accordingly, a person of ordinary skill in the art would immediately appreciate that, according to the protocols as described in Epstein et al, a DNA probe for a "potential duplicated regions of chromosome 21" can be used to identify the copy number of DNA sequences which is useful for the diagnosis of Down syndrome.

10. Prior to the earliest filing date of the present application, it was also well known in the art that a region in Band q22 of chromosome 21, which is defined by the three DNA sequences duplicated in two patients and includes D21S55, D21S3, and D21S15, is associated with clinical manifestations of DS including the physical features, congenital heart disease (CHD), and duodenal stenosis (DST). Korenberg et al., AM. J. Hum. Genet. 50: 294-302 (1992) (Exhibit 3, the Abstract). For example, one of the DNA probes, D21S15, was present in three DNA copies in DS patient DUP21JS (See Exhibit 3, p. 298, Figure 4; p. 299, Table 2). D21S15 was also present in three DNA copies in DS patients DUP21SOL and DUP21SM, both of whom manifested cardiac anomaly. Korenberg et al., Proc. Nat'l Acad. Sci. USA 91: 4997-5001 (1994) (Exhibit 4, p. 4998, Table 1 & p. 4999, Table 2). Accordingly, the aneuploidy for DNA probe D21S15 is associated with clinical features of DS such as CHD and/or DST.

11. The Specification of the above-identified application explicitly discloses the location of DS-CAM in Band q22 of Chromosome and the use of DS-CAM as a diagnostic marker. Examples of the disclosure include:

    A. The DS-CAM gene was isolated (as described in the Examples hereinafter) by using the BAC contig on 21q22.2 – q22.3 covering the region between D21S55 and MX1. The gene spans a minimum of 900 kb, estimated by summing the size of BACs and PACs that are non-overlapping and covered by the DS-CAM gene (Figure 1). (The Specification, p. 11, ll. 21-27).

B. The location and expression of DS-CAM in the Down Syndrome (DS) phenotype is supported by the studies of patients with partial trisomy 21. A subset of the DS features, including the typical facial appearance and mental retardation, were suggested by duplication of band 21q22 only. Other studies specifically mapped those features and congenital heart disease to the region 21q22.2 – q22.3 and between D21S 267 and MX1/MX2 (The Specification, p. 43, ll. 3-11).

C. The Figure 1 shows that DS-CAM is located in the Band q22 region from D21S55 through MX1, wherein probe D21S15 resides in the middle of DS-CAM (The Specification, Figure 1).

D. Nucleic acid molecules of DS-CAM or fragments thereof can be labeled with a readily detectable substituent and used as hybridization probes for assaying for the presence and/or amount of a DS-CAM or mRNA transcript in a given sample (The Specification, p. 12, ll. 11-15)(*emphasis added*).

E. Invention diagnostic systems are useful for assaying for the presence or absence of nucleic acid encoding DS-CAM in either genomic DNA or in transcribed nucleic acid (such as mRNA or cDNA) encoding DS-CAM (The Specification, p. 45, ll. 7-11).

F. The invention nucleic acids can be used for detecting a particular sequence encoding DS-CAM including the nucleotide sequences set forth in SEQ ID NO:1, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10, thereby diagnosing the presence of, or a predisposition for, holoprosencephaly, agenesis of the corpus callosum, or for several phenotypes of Down syndrome including mental retardation, and the like (The Specification, p. 45, l. 29 through p. 46, l. 1) (*emphasis added*).

12. In light of the foregoing, I conclude that one of ordinary skill in the art would immediately recognize that DS-CAM can be used as a molecular marker for the diagnosis of clinical features of DS including CHD and/or DST, in accordance with the teaching in the specification as well as the knowledge in the art as set forth in the prior art references.

A. According to Korenberg et al., Am. J. Hum. Genet. 47: 236 – 246 (1990)(Exhibit 1), a gene located in the Band q22 region assumes the role of being a molecular marker of DS. Since DS-CAM maps to the region in Band q22 from D21S55 through MX1, DS-CAM necessarily assumes the role of being a molecular marker for DS.

B. Korenberg et al. (1992 & 1994) teaches that three DNA copies of D21S15 are associated with clinical features of DS including CHD and/or DST (Exhibits 3 & 4). Since D21S15 is located in the middle of DS-CAM, DS-CAM itself is a DNA probe in the duplicated region of chromosome 21 which is associated with clinical features of DS including CHD and/or DST.

C. According to Epstein et al., Am. J. Hum. Genet. 49: 207-235 (1991) (Exhibit 2), a DNA probe in the duplicated region can be used to estimate the copy number of aneuploidy DNA in the region and thus diagnose the clinical features of DS using the Southern blot dosage analysis. Since DS-CAM is in the duplicated region of Band q22, naturally DS-CAM can be used to estimate the copy number of DNA in the region for the diagnosis of clinical features of DS including CHD and/or DST.

13. I hereby declare that all statements made herein of my own knowledge are true and all statements made based on references and belief are believed to be true; and further that there I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and, further, that these statements are made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of United States Applications No. 08/956,991, any patent issuing thereon, or any patent to which this verified statement is directed.

Executed and signed on 19 May, 2004,

at Los Angeles, California

Julie R. Korenberg

Julie R. Korenberg